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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/706,243	11/03/2000	George Norbert Cox III	019496-002220US	6940

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COOLEY GODWARD, LLP  
3000 EL CAMINO REAL  
5 PALO ALTO SQUARE  
PALO ALTO, CA 94306

EXAMINER

BRUSCA, JOHN S

ART UNIT	PAPER NUMBER
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1631

24

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application N .

09/706,243

Applicant(s)

COX ET AL.

Examiner

John S. Brusca

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 16 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 118-183 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 118-183 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 June 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) ✓ ✓
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 23,24.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ..

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### **DETAILED ACTION**

1. This supplemental Office action is being sent in response to the Response to Final Office Action filed 16 June 2003 because two Information Disclosure Statements were filed on or before the previous final Office action mailed 21 April 2003 but the Office action did not reflect the Information Disclosure Statements due to their not being matched to the application file. This supplemental Office action includes signed copies of the Form PTO 1449 for the Information Disclosure Statements filed 01 April 2003 and 21 April 2003. This supplemental Office action is also responsive to the Response to Final Office Action filed 16 June 2003. This supplemental Office action restarts the applicant's response time as noted below.

#### ***Drawings***

2. The formal drawings filed 16 June 2003 are accepted.

#### ***Response to Amendment***

3. The Response to Final Office Action filed 16 June 2003 contains a listing of pending claims in the revised amendment format patterned after the Electronic File Wrapper amendment format. The paper is improper because no indication of cancelled claims 1-117 is provided in the listing. Since no apparent amendment of the claims was intended by the applicants in the above submission the listing of the claims is not required or appropriate. The claims remain unaltered by the applicant's submission of 16 July 2003.

#### ***Claim Rejections - 35 USC § 112***

4. The rejection of claims 118-183 for lack of enablement for use of a zinc finger protein with two regulatory regions in the Office action mailed 06 August 2002 is withdrawn in view of

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the arguments presented in the response and declaration by Andreas Reik filed 12 February 2003.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 118-183 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of delivery of zinc finger proteins to cells by introduction of an expression vector, does not reasonably provide enablement for methods of delivery of zinc finger proteins to cells by introduction of exogenous zinc finger proteins to cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must regulate endogenous gene expression by delivery of a zinc finger protein to a cell. For the reasons

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discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The specification does not give specific guidance to deliver zinc finger proteins to cells and cause modulation of expression of an endogenous gene.

c) The specification does not provide working examples of delivery of zinc finger proteins to cells to cause modulation of expression of an endogenous gene.

d) The nature of the invention, regulation of gene expression by zinc finger proteins, is complex.

e) A search of the prior art does not show regulation of gene expression by delivery of zinc finger proteins to cells by any direct method.

f) The skill of those in the art of molecular biology is high.

g) The prior art does not address the predictability of the full scope of the claimed invention.

h) The claims are broad in that they read on (and in claims 136 and 179 specifically claim) embodiments that are not supported by the instant specification or the prior art.

In order to practice the claimed invention, the skilled practitioner would first turn to the teachings of the instant specification to practice embodiments of the claimed invention in which zinc finger proteins are delivered as protein to cells. However, the instant specification does not provide specific guidance or working examples of such embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art also does not provide such guidance. Finally, said practitioner would turn to trial and error experimentation to

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practice the full scope of the claimed invention without guidance from the specification or the prior art. Such represents undue experimentation.

7. Applicant's arguments filed 23 April 2002 have been fully considered but they are not persuasive. The applicants point to the declaration of Carl Pabo filed 12 February 2003. To the extent that the declaration expresses opinions without justification by evidence or reasoning the declaration is not persuasive. The declaration does point to articles by Phelan et al and Debs et al. Phelan et al. does not describe delivery of extracellular protein to cells. Rather Phelan et al. describes transfection of cells with expression vector polynucleotides that encode fusion proteins comprising HSV VP22 domains. These fusion proteins are then observed to spread to neighboring cells after expression of the vector. Phelan et al. is concerned with transport of proteins between cells rather than the claimed invention which reads on delivery of extracellular protein to cells. Debs et al. shows delivery of an extracellular transcription factor protein derived from a glucocorticoid receptor to cells and further shows that the transcription factor enhances expression from a transfected reporter gene vector. However Debs et al. uses only in vitro cultured cells, and shows only regulation of expression by a sensitive assay from a transfected reporter gene vector. Debs et al. does not show use of an engineered zinc finger protein, nor does Debs et al. show modulation of expression of an endogenous gene, as in the claimed invention. Further, Debs et al. teaches away from modulation of endogenous genes in the paragraph that bridges pages 10191-10192. Therefore neither Phelan et al. nor Debs et al. establish enablement for the embodiments of the claimed invention that add exogenous protein to cells.

8. Applicant's arguments filed 16 June 2003 have been fully considered but they are not persuasive. The applicants point to an abstract by Yeh et al. for support of enablement for protein

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delivery embodiments of the instant claims. Yeh et al. was published in May 2003, over 4 years later than the instant effective US filing date under 35 U.S.C. § 120. Yeh et al. states

“ we are able to show a 2.9-fold increase in VEGF-A mRNA levels when compared to delivery of IS alone and, for the first time, demonstrate that *peptide-mediated* delivery of an artificial transcription factor can upregulate specific VEGF-A endogenous gene expression *in vivo*.”

The assertion by Yeh et al. that the prior art has not previously shown peptide-mediated delivery of transcription factors serves to show that the instant application was not enabling for peptide-mediated delivery of zinc fingers. Yeh et al. is an abstract and is not an enabling reference. the Yeh et al. abstract does not show sufficient details of the isolation and structure of internalization sequences (IS) to enable one of skill in the art to perform the full scope of the claimed invention. The Yeh et al. abstract does not detail the amount of experimentation required to successfully isolate a functional IS peptide ant to further use it to facilitate entry of a zinc finger protein. The Yeh et al. abstract does not address the likelihood that any putative IS will be functional or the likelihood that any zinc finger protein can be introduced to a cell and function to regulate gene expression. The Yeh et al. abstract discusses only use of a cultured mouse 3T3 cell line and does not address introduction of zinc finger proteins in other cultured cell lines or animals. The applicants point to page 44, lines 7-25 for discussion of IS, but the discussion does not show the IS used by Yeh et al., and Yeh et al. teaches away from the antennapedia domain suggested in the instant specification at page 44.

### ***Claim Rejections - 35 USC § 103***

9. The applicants arguments regarding the rejection under 35 U.S.C. § 103 in the response filed 12 February 2003 are persuasive in part. The arguments presented that Liu et al.'96 does

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not show regulation of transcription is not persuasive because one of skill in the art would expect the unmodified exogenous zinc finger proteins of Liu '96 to operate by regulation of gene transcription because at the time of filing of the instant application the prior art, for example Choo et al. and Liu et al. '97, provided clear teachings that zinc finger proteins acted by modulation of gene transcription. The argument that the prior art did not show regulation of endogenous genes by engineered zinc finger proteins is persuasive because, as pointed out by the applicants in their response, the prior art such as Choo et al. and Liu et al. '97 showed use of reporter constructs as substrates for engineered zinc finger proteins. The use of reporter constructs in the prior art served to teach away from the use of endogenous genes as targets of action of engineered zinc finger proteins. The cited prior art does not provide motivation to use an endogenous gene as a target of action of an engineered zinc finger protein with a reasonable expectation of success.

10. The rejection of claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 under 35 U.S.C. 103(a) as being unpatentable over Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) in the Office action mailed 06 August 2002 is withdrawn.

11. The rejection of claims 139, 161, and 182 under 35 U.S.C. 103(a) as being unpatentable over, Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138,



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141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above and further in view of Berg (reference CJ in the Form PTO 1449 received 03 November 2000) in the Office action mailed 06 August 2002 is withdrawn.

12. The rejection of claims 131, 132, 154, 155, 175, and 176 under 35 U.S.C. 103(a) as being unpatentable over Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above, and further in view of Berg as applied to claims 139, 161, and 182 above and further in view of Mukhopadhyay et al. in the Office action mailed 06 August 2002 is withdrawn.

13. The rejection of claims 140, 162, and 183 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above and further in view of Berg (reference CJ in the Form PTO 1449 received 03 November 2000) as applied to claims 139, 161, and 182 above, and further in view of Jones et al. (newly cited) in the Office action mailed 06 August 2002 is withdrawn.

#### ***Double Patenting***

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

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harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 118-135, 137-178, and 180-183 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 89-107, 113, 114, 116-129, 131-136, 142, 143, 145-163, 169, 170, 172, and 173 of copending Application No. 09/229037.

The claims are drawn to a method of modulating transcription of an endogenous cellular gene comprising contacting the endogenous gene within a living cell with an engineered zinc finger protein that binds a target site in the endogenous gene with a  $K_d$  of less than 25 nM and functions to modulate expression of the endogenous gene.

Claims 89-107, 113, 114, 116-129, 131-136, 142, 143, 145-163, 169, 170, 172, and 173 of copending Application No. 09/229037 are drawn to a method of modulating transcription of an endogenous cellular gene comprising contacting the endogenous gene within a living cell with

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an expression vector encoding an engineered zinc finger protein that binds a target site in the endogenous gene with a  $K_d$  of less than 25 nM and functions to modulate expression of the endogenous gene.

Claims 89-107, 113, 114, 116-129, 131-136, 142, 143, 145-163, 169, 170, 172, and 173 of copending Application No. 09/229037 represent a species of the instant claimed genus of delivery method of a zinc finger protein to a target cell, and thus anticipates the claimed invention.

This is a provisional obviousness-type double patenting rejection.

16. Claims 141-183 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30, 31, 33-46, 48-62, and 91-93 of copending Application No. 09/478681. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims have limitations of regulation of developmentally silenced genes and other limitations which represent species of the instant generic claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 118-183 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20, 22-50, 52-78, and 80-88 of copending Application No. 09/897844. Although the conflicting claims are not identical, they are not patentably distinct from each other because the differences between the claims are minor.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Applicant's arguments filed 12 February 2003 have been fully considered but they are not persuasive. The applicants state that a restriction requirement in parent application No. 09/229037 serves to make the above double patenting rejection over application No. 09/229037 is improper. However, the instant and copending claims are both drawn to the same group of a method of using an expression vector to modulate expression of a target gene in a cell. The instant claims are generic as to the method of introduction of the zinc finger protein, and the claims of copending application No. 09/229037 are drawn to the species of introduction by transfection of an expression vector. Instant claims 136 and 139 limited to introduction of exogenous protein were not cited in the double patenting rejection over application No. 09/229037. Since it is well established that species anticipate a genus, the rejection is proper.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

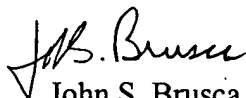
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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 703 308-4231. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703 308-4025. The fax phone numbers for the organization where this application or proceeding is assigned are 703 746-5137 for regular communications and 703 746-5137 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

  
John S. Brusca  
Primary Examiner  
Art Unit 1631

jsb  
June 25, 2003